A New Era: DIAN and the Secondary Prevention of Symptomatic AD

John C. Morris, MD

Harvey A. and Dorismae Hacker Friedman
Distinguished Professor of Neurology

Washington University in St. Louis
School of Medicine

DIAN
Dominantly Inherited Alzheimer Network

Knight ADRC
Alzheimer's Disease Research Center
WASHINGTON UNIVERSITY ST. LOUIS

Disclosure Statement (2011-2012)

- Sources of Research Support
  1. National Institute on Aging
     a) Alzheimer's Disease Research Center (ADRC; P50 AG05681; JCM, PI)
     b) Healthy Aging and Senile Dementia (HASD; P01 AG03991; JCM, PI)
     c) Adult Children Study (ACS: P01 AG026276; JCM, PI)
     d) Dominantly Inherited Alzheimer Network (DIAN; U19 AG032438; JCM, PI)
  2. Anonymous Foundation
  3. Alzheimer's Association
  4. Industry-sponsored clinical trials (Eli Lilly; Janssen Alzheimer Immunotherapy Program; Pfizer)

- Consulting Relationships
  1. Eisai
  2. Janssen Alzheimer Immunotherapy Program
  3. GlaxoSmithKline
  4. Novartis
  5. Pfizer

- Fees > $10,000

  None

- Stock Equity

  None

- Speaker's Bureaus

  None

- Editorial Boards

  Annals of Neurology

Introduction to Autosomal Dominant AD

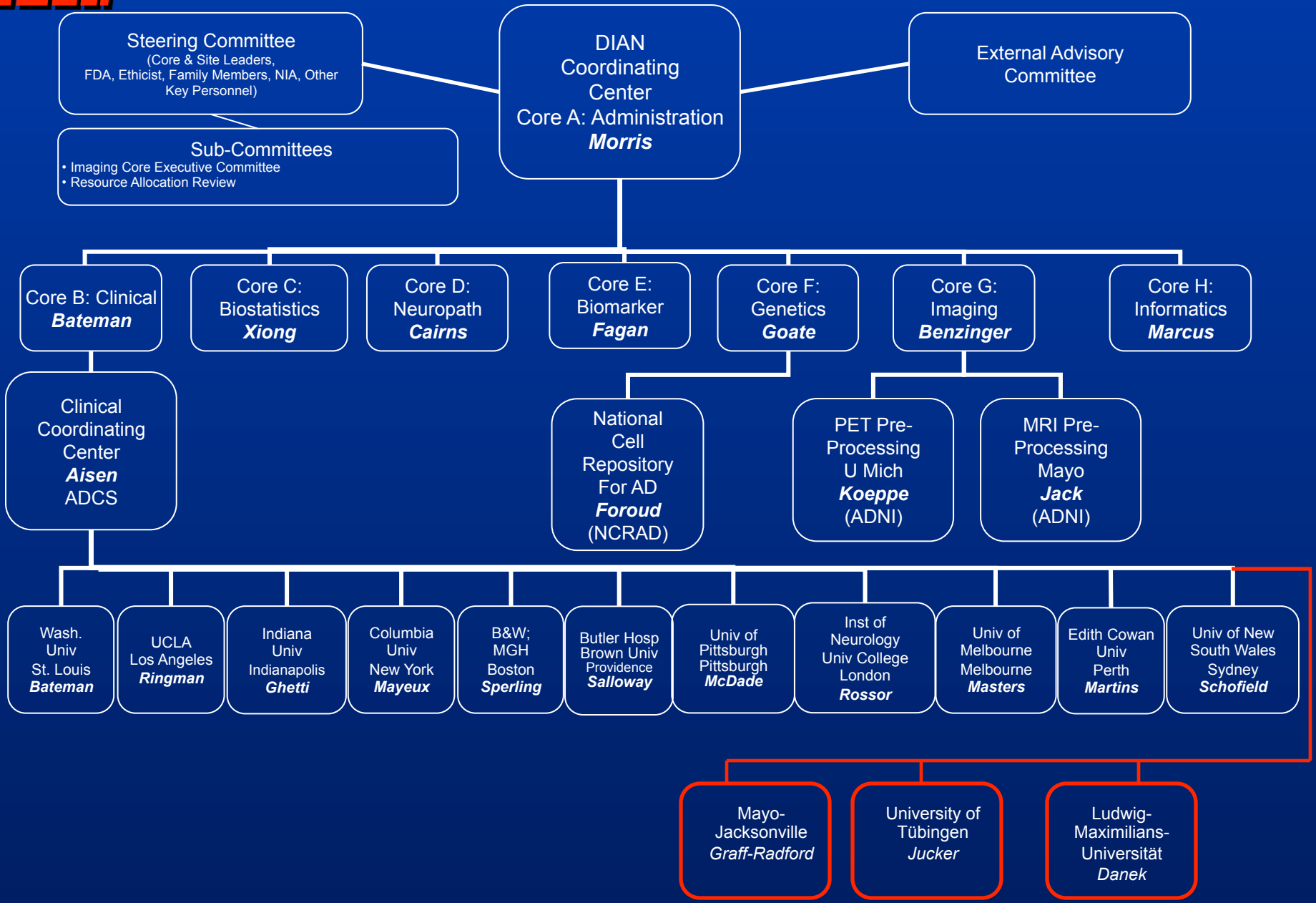
Measure	Autosomal Dominant AD	Sporadic AD
Clinical presentation	Amnestic	Amnestic
Course	Gradual cognitive and functional decline, plus motor signs and seizures	Gradual cognitive and functional decline
MRI	Hippocampal and whole brain atrophy	Hippocampal and whole brain atrophy
PIB PET	Cortex plus basal ganglia	Cortex
FDG PET	Parieto-occipital hypometabolism	Parieto-occipital hypometabolism
CSF Aβ 42	Decreased by 50%	Decreased by 50%
CSF tau	Increased by 2-fold	Increased by 2-fold

Original DIAN Aims

DIAN
Dominantly Inherited Alzheimer Network

- Determine WHEN the pathobiology of AD begins in asymptomatic mutation carriers (*PSEN1*, *PSEN2*, *APP*) in relation to parental age of onset of dementia
- Determine the SEQUENCE and RATE of the pathobiological changes
- Compare the clinical and pathological phenotypes of dominantly inherited AD with late onset AD
- Enroll and study longitudinally with a uniform protocol 400 persons (~200 MCs, ~200 NCs) from families with a known pathogenic mutation for AD

DIAN Organizational Chart *(U19 AG032438, JC Morris, PI)*



DIAN Assessments

Procedure	Initial Visit	Follow-up Visit*
Study explanation	X	
Consent	X	
Blood for Genetic Analysis	X	
Blood for Biochemical biomarkers	X	X
Inclusion and Exclusion Criteria	X	
Demographics, Family History, Medical History, Physical Exam, Neurological Exam, UPDRS	X	X
Clinical Evaluation – CDR, GDS, NPI, FAQ (Lifestyle), Hollingshead, Hachinski, Exercise questionnaire	X	X
Psychometric Battery – MMSE, Logical Memory Test IA & IIA, Digit Span Test (forward and backward), Category Fluency Test, Trail Making Test (Parts A & B), Boston Naming Test, Letter Fluency, WAIS-R Digit Symbol, Word List Immediate and Delayed Recall, IPIP, Computerized Cognitive Battery	X	X
MRI-3T	X	X
FDG-PET	X	X
PIB-PET	X	X
Lumbar Puncture for Cerebrospinal Fluid	X	X
* Participants and collateral sources not seen annually have a yearly telephone interview		

DIAN Enrollment Report

Over Years 01-06, sites will recruit, enroll and follow these individuals to reach a sample size of 400 participants

	Initial Visits Actual	Follow-up Visits In-Person	Follow-up Visits Remote
Year One (9/2008-6/2009)	11	0	0
Year Two (7/2009-6/2010)	76	0	7
Year Three (7/2010-6/2011)	103	26	41
Year Four (7/2011 - 5/15/2012)	66	41	61
YTD TOTALS	**256**	**67**	**115**

Participant Entry Characteristics

	Asymptomatic 188 (72.9%)		Symptomatic 70 (27.1%)	
N = 258* *(Target 80% Asymptomatic, 20% Symptomatic) (*Table based on 212 participants. **46** Mutations in Process- Missing)*	MUT: 149		MUT: 63	
	74 (NC-)	75 **(MC+)**	5 (NC-)	58 **(MC+)**
Age	41.1 (SD 9.0)	34.4 (SD 9.0)	41.8 (SD 14.9)	45.5 (SD 10.5)
Gender (% Female)	44 (59.5%)	44 (58.7%)	3 (60%)	32 (55.2%)
Parental Age of Onset	46.4 (SD 6.9)	47.4 (SD 6.6)	46.2 (SD 8.5)	45.1 (SD 10.6)
Education	14.7 (SD 2.5)	14.4 (SD 2.6)	13.4 (SD 2.8)	13.7 (SD 2.5)
MMSE	29.3 (SD 1.1)	29.0 (SD 1.4)	29.2 (SD 0.8)	22.7 (SD 6.9)
ApoE4+ ***1 E4***	21	15	0	11
2 E4	0	1	0	4

MC = Mutation Carrier; NC = Non-carrier

*Table statistics based on 212 participants with NCRAD confirmed mutation data available as of 22 MAY 2012

Procedure Completion Rates

Initial Visit Procedures Completed	**Totals N= 256**
Psychometric *(E-Prime and UDS Uploaded)*	240 (94%)
Genetics Blood	256 (100%)
NCRAD Blood	256 (100%)
MRI *(Acquired)*	241 (94%)
PET PIB *(Acquired)*	233 (91%)
FDG PET *(Acquired)*	234 (91%)
Lumbar Puncture	208 (82%)
Fasted Serum and Plasma	247 (96%)

DIAN Mutation Distribution
(based on data from January 25, 2012)

Gene	Frequency
PSEN1	91 (77.8%)
PSEN2	9 (7.7%)
APP	17 (14.5%)

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 30, 2012 N Engl J Med 2012;367:795-804.

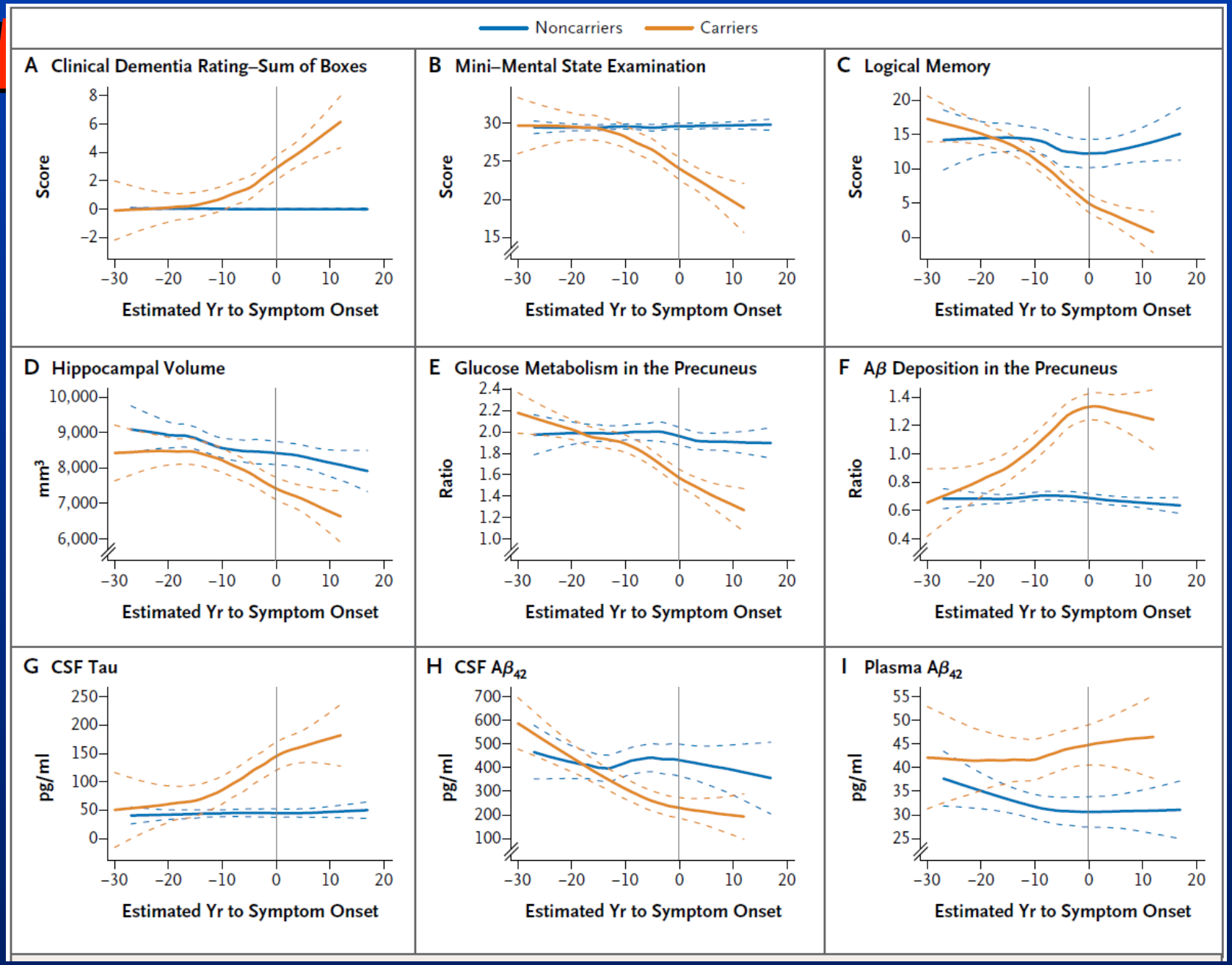
Clinical and Biomarker Changes in Dominantly Inherited Alzheimer's Disease

Randall J. Bateman, M.D., Chengjie Xiong, Ph.D., Tammie L.S. Benzinger, M.D., Ph.D., Anne M. Fagan, Ph.D., Alison Goate, Ph.D., Nick C. Fox, M.D., Daniel S. Marcus, Ph.D., Nigel J. Cairns, Ph.D., Xianyun Xie, M.S., Tyler M. Blazey, B.S., David M. Holtzman, M.D., Anna Santacruz, B.S., Virginia Buckles, Ph.D., Angela Oliver, R.N., Krista Moulder, Ph.D., Paul S. Aisen, M.D., Bernardino Ghetti, M.D., William E. Klunk, M.D., Eric McDade, M.D., Ralph N. Martins, Ph.D., Colin L. Masters, M.D., Richard Mayeux, M.D., John M. Ringman, M.D., Martin N. Rossor, M.D., Peter R. Schofield, Ph.D., D.Sc., Reisa A. Sperling, M.D., Stephen Salloway, M.D., and John C. Morris, M.D., for the Dominantly Inherited Alzheimer Network

Developing an international network for Alzheimer's research: the Dominantly Inherited Alzheimer Network

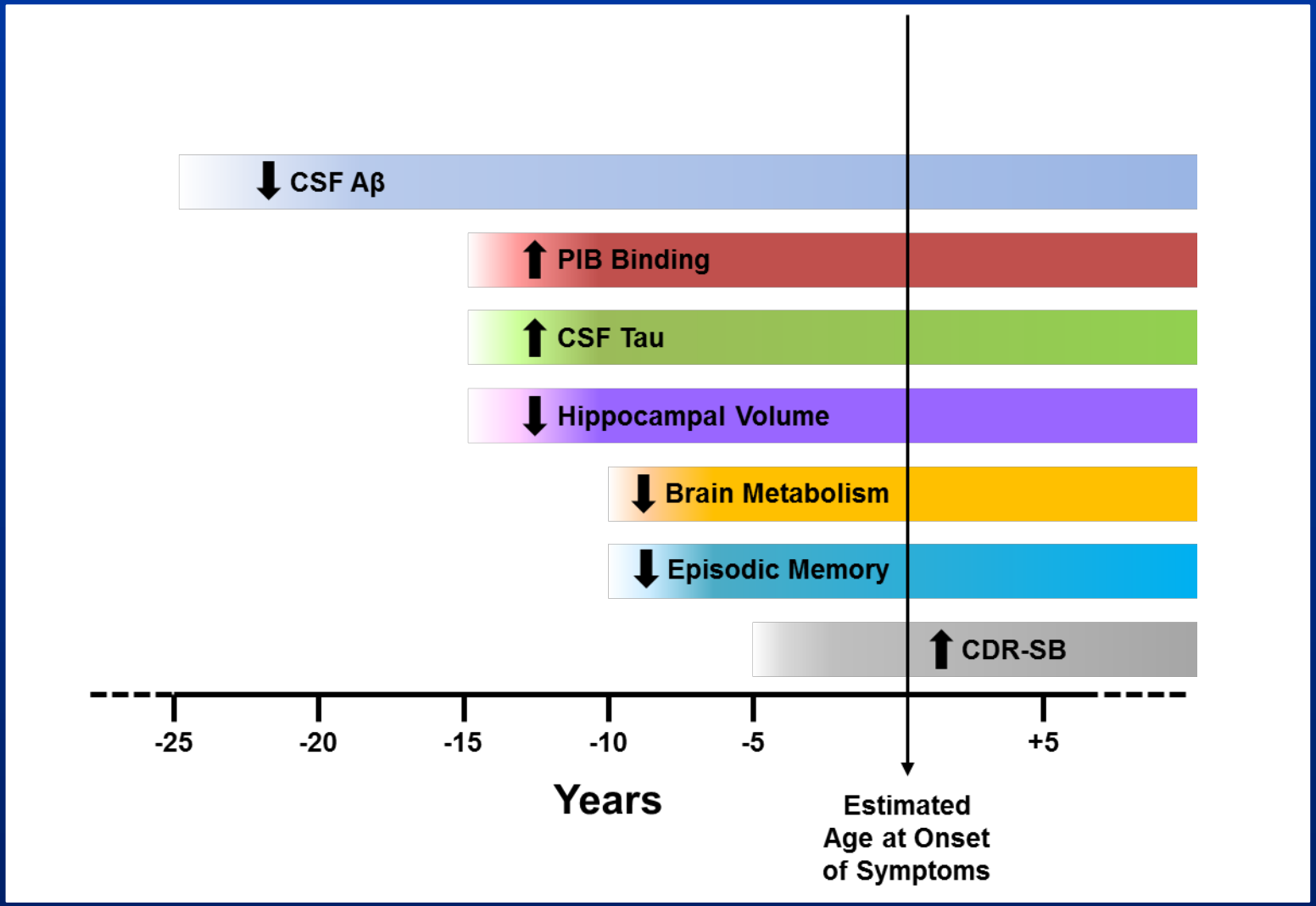
Clin. Invest. (2012) 2:975-984.

John C Morris*, Paul S Aisen, Randall J Bateman, Tammie LS Benzinger, Nigel J Cairns, Anne M Fagan, Bernardino Ghetti, Alison M Goate, David M Holtzman, William E Klunk, Eric McDade, Daniel S Marcus, Ralph N Martins, Colin L Masters, Richard Mayeux, Angela Oliver, Kimberly Quaid, John M Ringman, Martin N Rossor, Stephen Salloway, Peter R Schofield, Natalie J Selsor, Reisa A Sperling, Michael W Weiner, Chengjie Xiong, Krista L Moulder, & Virginia D Buckles



Bateman et al., NEJM 2012

Alzheimer Biomarker Pathochronology in Autosomal Dominant AD



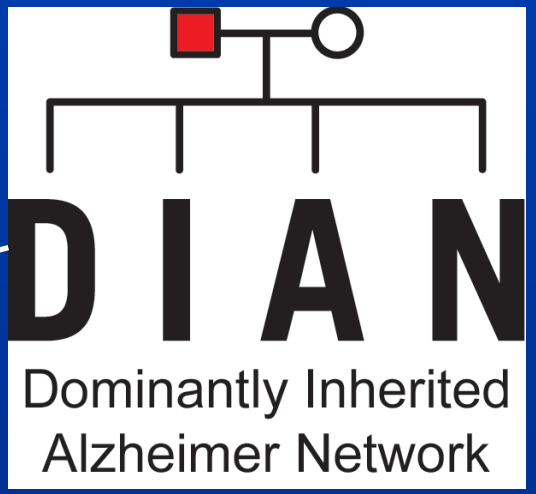
Morris et al., Clin Invest 2012; 2:975-984

Interim Conclusions

- As of 12/1/12, over 300 participants are enrolled in DIAN
- The clinical, cognitive, imaging, and biochemical biomarkers of AD in mutation carriers are similar to those for late-onset sporadic AD and can be detected at least **20 years** before estimated age of onset of dementia
- The first clinical and cognitive changes begin at least **5 years** prior to estimated age of onset of dementia
- The DIAN cohort is well-suited for proof-of-concept studies (drug effect on biomarkers) and for dementia prevention studies in asymptomatic mutation carriers

Rationale for Treatment Trials in Individuals at Risk for Autosomal Dominant Alzheimer Disease

- Current therapeutic trials may be too late: proposed therapeutics to slow or halt underlying AD are unlikely to reverse the extensive neuronal death already present at symptomatic onset
- Certain risk (~100%) with mutation in *PSEN1*, *PSEN2,* or *APP* for symptomatic AD enables prevention studies
- Disease modifying therapeutics are largely developed with animal models based on human disease-causing mutations. AD caused by these known mutations may be most likely to respond to the proposed treatments
- Results from treatment trials in ADAD will help support or refute the “amyloid hypothesis” of AD



alzheimer's association®

DIAN TU is a public/private partnership, directed by R Bateman (WU TU Team: V Buckles, M Carril, D Clifford, D Levitch, S Mills, J Morris, K Moulder, A Oliver, A Santacruz, N Selsor, W Sigurdson, and J Snider)

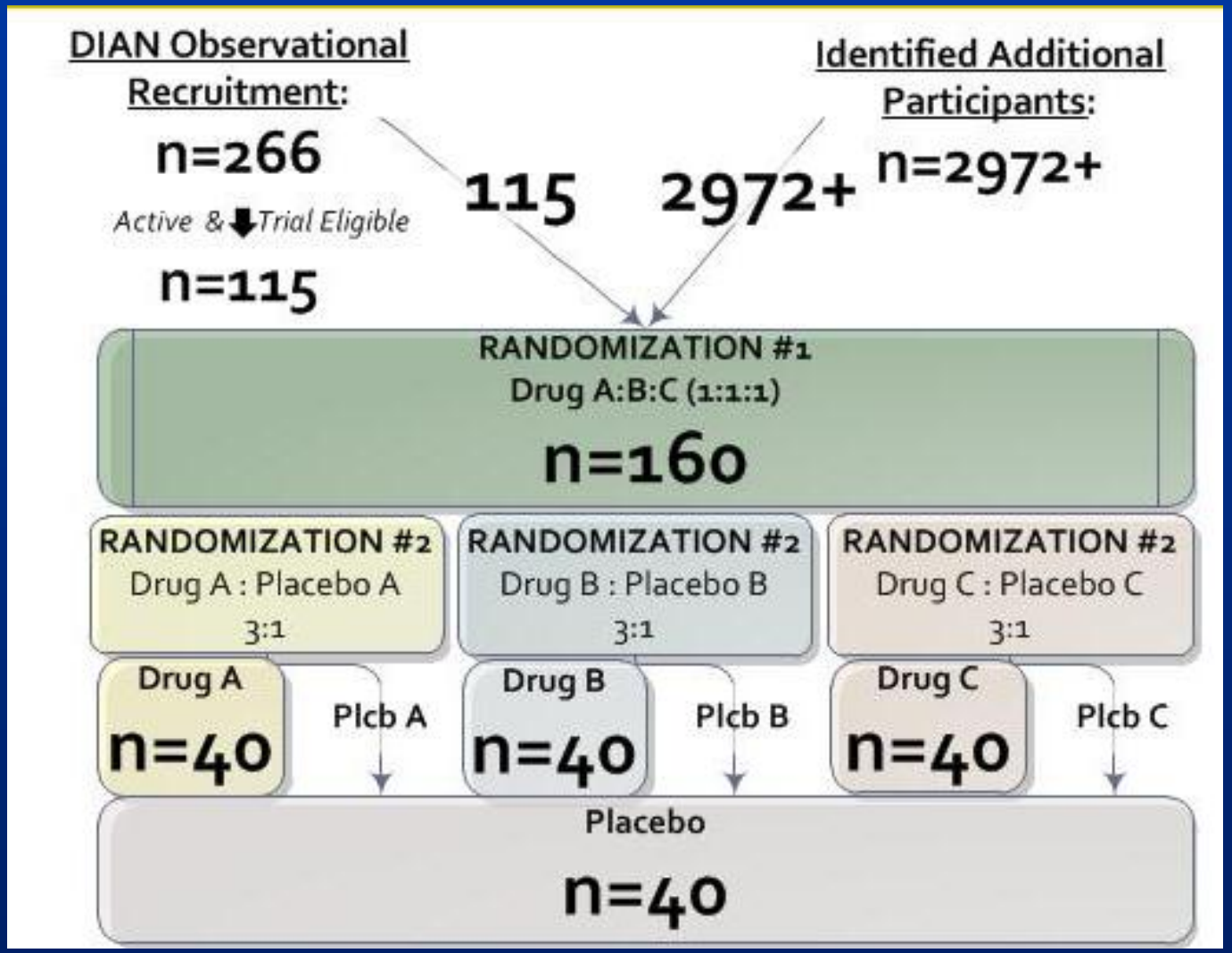
DIAN Pharma Consortium

biogen idec
élan
Genentech
A Member of the Roche Group
janssen
ALZHEIMER'S IMMUNOTHERAPY PROGRAM
INNOVATION TO REMEMBER™
Pfizer
Lilly
Mithridion
NOVARTIS
Pfizer
Roche
SANOFI

Therapy Evaluation

- Therapy evaluation process is ongoing
- DIAN TTU continues to accept nominations
- Therapy Evaluation Committee typically meets every 4 months to re-evaluate compounds and review new nominations
- Factors considered by evaluation committee include stage of clinical development, likelihood of efficacy, side-effect/adverse event profile, commitment of availability

Randomization of Mutation Carriers in DIAN Trials



Clinical Study Protocol: Assessments

PROCEDURE	Baseline, Yr 1 & 2	Every 3 mo.	Every mo.
Informed consent	X		
Med/Tx Hx	X		X
Clinical Assessment	X		
PE & Neuro Exam	X		
Vitals	X		X
12-lead ECG	X	X	
C-SSR	X		
Genetics/ApoE	X (b-line)		
Hem/Chem/LFTs/UA	X	X	
Preg testing	X		X
Cognitive Testing	X		
vMRI, PET: PIB & FDG	X		
Safety MRI	X	X	
LP-CSF	X		
AE/SAE Assmt	X		X
Study Drug Admin	X		X

DIAN Trials Summary

- Participants and families eager for clinical trials
- Strong scientific rationale for DIAN treatment trials
- Regulatory agencies (FDA and EMA) supportive of ADAD prevention trials
- Fifteen DIAN therapeutic nomination packets have been received from Pharma
- DIAN Pharma Consortium supports and assists with clinical trial design – currently 10 Pharma company members
- DIAN Trials Unit formed to design, implement and manage DIAN treatment trials
- First studies targeted to start in early 2013

Planned "Secondary Prevention" Trials for AD (US Initiatives)

- Autosomal dominant early onset AD
  - Alzheimer's Prevention Initiative, E Reiman and P Tariot, Banner Health: **Crenezumab** (Genentech) in Colombian E280A kindred (plus other mutations in NA)
  - DIAN Trials Unit, R Bateman and DIAN: **Solanezumab** (Lilly); **Gantenerumab** (Roche); **BACE inhibitor** (Lilly) in the international DIAN cohort (multiple mutations)
- "Sporadic" late onset AD
  - Anti-Amyloid Treatment in Asymptomatic AD (A4), R Sperling, P Aisen, and ADCS (currently selecting mab)
  - [Zinfandel: **Pioglitazone** (Takeda)]

THANK YOU

www.dian-info.org